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CORRELATIONS BETWEEN CLINICAL, BIOLOGICAL, AND HISTOPATHOLOGICAL CHARACTERISTICS AND EARLY POSTOPERATIVE OUTCOMES IN COMPLICATED COLON CANCER

DOCTORAL THESIS ABSTRACT

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INTRODUCTION

Colon cancer is a major public health concern because of its high incidence and associated mortality. Despite advances in screening, early diagnosis, and multimodal oncological treatment, many patients still present to emergency departments with complicated forms of the disease [1]. Bowel obstruction, tumor perforation with secondary peritonitis, and lower gastrointestinal bleeding are the three main acute complications of colon cancer and require the prompt establishment of an appropriate therapeutic strategy [2].

In such situations, surgical management differs fundamentally from elective surgery. It focuses on the rapid control of obstruction, sepsis, hemorrhage, or hemodynamic instability, with the primary objective of saving the patient's life, even when this may compromise long-term oncological outcomes, restoration of gastrointestinal continuity, or quality of life. [3].

Patients with complicated colon cancer are often elderly and have multiple comorbidities, frequently compounded by fluid and electrolyte disturbances, sepsis, organ failure, and systemic inflammation, a central component of tumor progression and carcinogenesis [4]. The interaction among these factors reduces physiological reserve and increases the risk of postoperative complications, reinterventions, prolonged hospitalization, and early mortality [5].

Systemic inflammation provides a link between carcinogenesis, tumor progression, and postoperative outcomes. The inflammatory response generated by both the malignant tumor and obstruction, ischemia, perforation, peritoneal contamination, or sepsis may further enhance the patient's biological imbalance [4] and promote the development of early postoperative complications.

Although inflammation has been assessed using routine biological parameters such as C-reactive protein, the neutrophil-to-lymphocyte ratio, the platelet-to-lymphocyte ratio, and the systemic immune-inflammation index, most studies have focused on elective colon cancer surgery and other gastrointestinal malignancies. The role of these markers in emergency setting for complicated colon cancer remains insufficiently defined [6]. In this context, the present thesis aimed to determine whether these parameters can predict the risk of postoperative complications, anastomotic leakage, and mortality and whether they can contribute to individualized surgical decision-making.

I. GENERAL PART

1. The Influence of Inflammation on the Development and Progression of Colon Cancer

The development of colon cancer is a complex process driven by the progressive accumulation of genetic and epigenetic alterations, in association with the effects of environmental factors and the tumor microenvironment [7]. Malignant transformation of the colonic epithelium frequently involves disruption of the WNT signaling pathway and the APC gene [8], followed by additional alterations in other proto-oncogene such as KRAS, TP53, or TGFBR2 [7].

Chronic inflammation may contribute both to the initiation of carcinogenesis and to the survival of neoplastic clones. Inflammatory cells present into the tumor microenvironment can release cytokines, growth factors, and reactive oxygen and nitrogen species, which may cause DNA damage, genomic instability, and altered gene expression [9]. Activation of signaling pathways such as NF-κB and JAK/STAT stimulates tumor-cell proliferation and survival, angiogenesis, tissue invasion, and suppression of the antitumor immune response [10].

2. Complications During the Course of Colon Cancer

A substantial proportion of patients with colon cancer present to emergency departments with bowel obstruction, tumor perforation, or lower gastrointestinal bleeding. The occurrence of these complications is influenced by tumor location and size, local extension, histological characteristics, and time of diagnosis [11].

Bowel obstruction is the most common presentation for complicated colon cancer. Left-sided tumors, particularly sigmoid tumors, cause obstruction more frequently because of the narrower luminal caliber and the firmer consistency of the intestinal content[12]. Progressive distension leads to fluid and electrolyte inbalances, dehydration, bacterial translocation, and impaired perfusion of the bowel wall and in some cases may progress to ischemia, necrosis, and diastatic perforation of the cecum [13].

Perforation may occur at the tumor and is associated with peritoneal contamination, peritonitis, and sepsis. Free perforation is associated with a poorer prognosis than localized perforation because it causes extensive abdominal contamination and rapid clinical deterioration [14]. In such cases, the primary therapeutic objective in such cases is the control of the septic source at the expense of oncological outcomes[15].

Lower gastrointestinal bleeding is another complication of colon tumors and may range from chronic blood loss resulting in anemia to acute hemorrhage associated with hemodynamic instability. Although severe bleeding is relatively uncommon, it may require emergency surgical intervention

3. Management of Colon Cancer in emergency setting

The treatment of complicated colon cancer must be individualized according to tumor location, the mechanism of the complication, the degree of peritoneal contamination, hemodynamic stability, organ function, and patient comorbidities. Unlike elective surgery, complete staging and adequate preoperative optimization are not always possible[16].

For obstructing right-sided colon tumors, right hemicolectomy with primary anastomosis may be performed in stable patients with adequate tissue perfusion and no severe peritoneal contamination. For left-sided tumors, options include resection with primary anastomosis, Hartmann's procedure, subtotal colectomy, or creation of a diverting stoma. The choice depends on the severity of obstruction, the viability of the proximal colon, and the estimated risk of anastomotic leakage [17].

Endoscopic stenting may be used in selected patients with obstructing tumors, either for palliation or as a bridge to elective surgery. This strategy permits colonic decompression, correction of biological imbalances, and subsequent surgery under elective conditions. Its use depends, however, on the availability of endoscopic expertise and on avoidance of perforation [18].

In tumor perforation, treatment is focused on controlling sepsis through resection of the affected segment, peritoneal lavage, and drainage. In unstable patients with generalized peritonitis or organ failure, stoma formation may be safer than primary anastomosis [19]. In tumor-related bleeding, the indication for and extent of surgery are determined by the severity of blood loss, the feasibility of endoscopic control, and the oncological status [17].

4. Postoperative Complications in Colon Cancer Surgery

Emergency surgery for colon cancer is associated with a high rate of early complications because of abdominal contamination, systemic inflammation, metabolic disturbances, and comorbidities [20]. The main surgical complications are anastomotic leakage, surgical-site infection, anastomotic bleeding, and early stoma-related complications [16].

Anastomotic leakage is one of the most severe complications and results from the interaction between technical and patient-related factors. Hypoperfusion, vasopressor therapy, sepsis, obesity, anemia, renal failure, peritoneal contamination, and systemic inflammation may impair anastomotic healing [21]. Clinical manifestations range from low-output leaks and localized collections to generalized peritonitis and multiple-organ failure [22].

Surgical-site infections are promoted by the contaminated nature of the procedure, prolonged operative time, diabetes, obesity, and impaired immune status. They may progress from superficial infection to fascial dehiscence and evisceration. Early stoma complications include ischemia, necrosis, retraction, bleeding, edema, and peristomal abscesses, some of which require reoperation [16].

Stoma formation following colonic resection is a feasible option, but it is associated with reduced quality of life and, in some cases, contact dermatitis, mucocutaneous separation, and ischemia of the exteriorized bowel segment. These complications entail additional costs and an increased risk of reoperation [23].

II. SPECIAL PART. PERSONAL CONTRIBUTION

5. Research hypothesis and primary objectives

The general objective of the research was to assess the ability of selected clinical, biological, inflammatory, and histopathological parameters to predict the early postoperative course of patients undergoing emergency surgery for complicated colon cancer. An additional objective was to investigate the usefulness of these parameters in intraoperative decision-making, particularly when choosing between primary anastomosis and stoma formation.

The working hypothesis was based on the bidirectional relationship between inflammation and carcinogenesis. Inflammation may contribute to the initiation and progression of neoplasia, whereas the tumor, together with its complications, may generate an intense systemic inflammatory response. Elevated preoperative inflammatory markers, including C-reactive protein, the neutrophil-to-lymphocyte ratio, the platelet-to-lymphocyte ratio, and the systemic immune-inflammation index, were hypothesized to be associated with comorbidities,

organ dysfunction, and severe clinical presentations, as well as with a higher frequency and greater severity of postoperative complications and increased mortality. The study also examined whether integrating these variables could support individualized operative decision-making.

The specific objectives were to characterize the demographic and clinical profile of patients with complicated colon cancer; identify the main evolutive complications of this neoplasia; assess comorbidities and clinical severity at admission; analyze the topographic distribution and histopathological characteristics of the tumors; describe the surgical procedures performed; and determine the main early postoperative complications.

Two complementary studies were conducted to achieve these objectives. The first assessed the predictive value of clinical and inflammatory parameters for the risk of early postoperative complications. The second analyzed the influence of preoperative clinical and laboratory markers on operative strategy, the risk of anastomotic leakage, and early mortality.

6. General Research Methodology

This observational, retrospective, single-center, non-randomized study included patients diagnosed with complicated colon cancer who underwent emergency surgery in the Department of General Surgery at "Sfântul Pantelimon" Clinical Emergency Hospital, Bucharest, between October 2020 and November 2025. The study period included both the COVID-19 pandemic and subsequent years, during which delayed presentations and complicated oncological disease remained frequent.

Data were extracted from medical records, operative reports, histopathology reports, and the hospital information system. The study was conducted after approval by the Ethics Committee of "Sfântul Pantelimon" Clinical Emergency Hospital (Approval No. 102, January 27, 2025) and in accordance with the principles of the Declaration of Helsinki.

Patients older than 18 years who presented with one of the major complications of colon cancer—bowel obstruction, tumor perforation, or lower gastrointestinal bleeding—underwent emergency surgery, and had histopathological confirmation of malignancy were included.

Patients undergoing elective surgery for uncomplicated disease, those with benign colonic tumors, colonic metastases from other malignancies, locoregional recurrence, no histopathological confirmation, refusal of surgical treatment, synchronous tumors, intraoperative death, or incomplete medical documentation were excluded. Analyses of inflammatory markers additionally excluded patients with hematological disorders, autoimmune diseases,

immunodeficiency, orother treatments capable of significantly altering complete blood count parameters.

After applying the inclusion and exclusion criteria, 221 patients were included in the overall cohort, all of whom underwent open surgery. For the second study, 217 patients were analyzed after excluding cases in which tumor resection could not be performed or the study-specific methodological criteria were not fulfilled.

Demographic datas included age, sex, and area of residence. Clinical assessment included body mass index, Charlson Comorbidity Index, history of congestive heart failure and diabetes mellitus,type of complication present, presence of systemic inflammatory response syndrome, organ failure, and the need for vasopressor therapy.

Preoperative laboratory data included leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts, as well as hemoglobin, C-reactive protein, urea, and creatinine levels. The neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic immune-inflammation index were calculated from the complete blood count.

Operative variables included the ASA class, tumor location, the presence of perforation and degree of peritoneal contamination, hepatic or peritoneal metastases, type of resection and the choice between primary anastomosis and stoma formation.

Postoperative outcomes were assessed according to the occurrence, type, and severity of early surgical complications based on the Clavien–Dindo classification, the need for reoperation, length of hospital stay, and postoperative mortality. Abdominal-wall complications, anastomotic leakage, and early stoma-related complications were analyzed separately.

Histopathological assessment included histological type, tumor grade, T and N stages, and the presence of lymphovascular or perineural invasion. Integration of these data was intended to distinguish the contributions of the patient’s biological status, the inflammatory response, and tumor aggressiveness to postoperative outcomes.

Statistical analysis was performed using IBM SPSS Statistics, version 26. Continuous variables were expressed as means and standard deviations and compared using Student’s t-test, analysis of variance, Welch’s ANOVA, or nonparametric tests, depending on their distribution. Categorical variables were reported as frequencies and percentages, and associations between groups were evaluated using the chi-square test or Fisher’s exact test.

Variables that were significant in univariate analyses were entered into binary logistic

regression models while respecting the ratio between the number of events and the number of predictors included. Results were expressed as odds ratios with 95% confidence intervals.

The discriminatory ability of individual markers and multivariable models was evaluated using receiver operating characteristic curves. Optimal cutoff values were calculated using the Youden index, and performance was quantified by the area under the curve. Kaplan–Meier curves and the log-rank test were used for survival analysis.

7. Results

Two complementary analyses were performed in patients who underwent emergency surgery for complicated colon cancer. The first study sought to identify clinical, biological, inflammatory, and histopathological factors associated with the occurrence and severity of early postoperative complications. The second evaluated the influence of the same parameters on operative strategy, particularly the choice between primary anastomosis and stoma formation, and on the risk of anastomotic leakage and postoperative mortality.

After application of the general inclusion and exclusion criteria, the first study included 221 patients. The second study analyzed 217 patients after excluding cases that did not meet the specific methodological criteria regarding the type of resection

7.1. Demographic and Clinical Characteristics of the Cohort

Of the 221 patients, 128 were men (57.9%) and 93 were women (42.1%). The mean age was 69.57 years, with a range of 37–94 years. The largest age group was 70–79 years, comprising 69 patients (31.2%), followed by the 60–69-year group with 61 patients and the 80–89-year group with 48 patients.

The demographic distribution was similar in the second study of 217 patients. Of these, 126 were men (58.1%) and 91 were women (41.9%). The mean age was 69.32 ± 11.56 years, with the same range of 37–94 years.

Bowel obstruction was the main complication present in both cohorts and was identified in 107 and 105 patients, respectively. Lower gastrointestinal bleeding accounted for more than 24% of cases, whereas peritonitis secondary to tumor perforation occurred in fewer than 20%.

Systemic inflammatory response syndrome was identified in approximately one-quarter of patients. In the first study, 61 patients (27.6%) met the SIRS criteria, 56 (25.3%) required vasopressor therapy, and 69 (31.2%) had single- or multiple-organ failure. Acute kidney injury was the most common form of organ dysfunction.

In the cohort of 217 patients, SIRS was present in 58 cases (26.7%), organ failure in 66 patients (30.4%), and vasopressor therapy was required in 54 patients (24.9%).

Cardiovascular comorbidities were common. In the first cohort, 132 patients (59.7%) had hypertension, arrhythmias, or a history of congestive heart failure. The mean Charlson Comorbidity Index was above 6.5 points in both cohorts, with values ranging from 2 to 11. Body mass index ranged from 15.30 to 43.25 kg/m².

7.2. Preoperative Biological and Inflammatory Parameters

In the overall cohort, the mean leukocyte count was 11.95 ± 6.50 ×10⁹/L, the neutrophil count was 9.72 ± 6.68 ×10⁹/L, the lymphocyte count was 1.63 ± 1.16 ×10⁹/L, and the platelet count was 370.68 ± 149.89 ×10⁹/L. Mean hemoglobin was 11.13 ± 3.38 g/dL.

The mean neutrophil-to-lymphocyte ratio was 7.72 ± 6.11, the systemic immune-inflammation index was 3245.27 ± 4002.70, and the platelet-to-lymphocyte ratio was 323.12 ± 282.12. Mean C-reactive protein was 90.04 ± 97.70 mg/L. Mean serum urea was 56.78 ± 38.89 mg/dL, and mean creatinine was 1.24 ± 0.74 mg/dL.

Values recorded in the second cohort were comparable. The mean leukocyte count was 11.94 ± 6.50 ×10⁹/L, the neutrophil count was 9.71 ± 6.73 ×10⁹/L, the lymphocyte count was 1.63 ± 1.16 ×10⁹/L, and the platelet count was 368.87 ± 149.42 ×10⁹/L. The mean NLR was 7.74 ± 6.15, the SII was 3234.50 ± 4028.58, and the PLR was 321.75 ± 282.39. Mean CRP was 89.03 ± 97.13 mg/L, urea was 56.50 ± 38.99 mg/dL, and creatinine was 1.24 ± 0.75 mg/dL.

7.3. Tumor Characteristics and Surgical Procedures

The sigmoid colon was the most common tumor location, followed by the cecum. In the first study, sigmoid tumors were identified in 72 cases and cecal tumors in 51. The transverse colon was the least common site, accounting for 13 cases. In the second study, 68 patients had sigmoid tumors, 51 had cecal tumors, and only 13 had tumors of the transverse colon.

Most patients had a high anesthetic and surgical risk, with the majority classified as ASA III or ASA IV. Fewer than 10% of patients were classified as ASA II, and ASA V accounted for less than 5% of patients across both cohorts.

In the first study, tumor resection was feasible in 98.2% of patients. Primary anastomosis was performed in 136 patients (61.5%). The remaining patients underwent ileostomy or colostomy, depending on the type of resection and tumor location.

In the cohort of 217 patients, left hemicolectomy was the most common procedure and

was performed in 74 patients (34.1%). Right hemicolectomy was performed in 60 patients (27.6%), subtotal colectomy in 41 (18.9%), extended right hemicolectomy in 35 (16.1%), and total colectomy in 7 (3.2%). Gastrointestinal continuity was restored by primary anastomosis in 133 patients (61.3%), while 84 patients (38.7%) required stoms.

7.4. Analysis of Clinical Parameters in Relation to the Risk of Early Postoperative Complications

Of the 221 patients in the first study, 90 (40.7%) developed one or more postoperative surgical complications, whereas 131 (59.3%) had an uncomplicated postoperative course. Patients with complications had a significantly higher Charlson score than those without complications (7.58 ± 1.90 vs. 6.20 ± 1.91; $p < 0.0001$). Congestive heart failure was present in 50.0% of patients with complications compared with 16.8% of those with an uncomplicated course ($p < 0.0001$). Type 2 diabetes mellitus was identified in 42.2% of patients with complications and 12.2% of those without complications ($p < 0.0001$).

Vasopressor therapy was required in 40.0% of the complicated group and 15.3% of the uncomplicated group ($p < 0.0001$). Organ failure was present in 53.3% of patients with complications compared with 16.0% of those without complications ($p < 0.0001$), while SIRS was present in 43.3% and 16.8%, respectively ($p = 0.0001$).

Analysis of patients who developed complications showed significant differences among cinical presentation. Tumor perforation was identified in 35.6% of patients with complications and only 6.9% of those with an uncomplicated course ($p < 0.0001$). Lower gastrointestinal bleeding was more frequent in the uncomplicated group than in the complicated group (30.5% vs. 16.7%; $p = 0.0191$). Bowel obstruction did not differ significantly between groups.

7.5. Analysis of Laboratory Parameters in Relation to the Risk of Early Postoperative Complications

Patients with a complicated postoperative course had significantly higher inflammatory markers and renal function parameters. Mean leukocyte count was 13.76 ± 8.14 $\times 10^9$/L in the complicated group versus 10.70 ± 4.71 $\times 10^9$/L in the uncomplicated group ($p = 0.0005$). Mean neutrophil counts were 11.38 ± 7.60 $\times 10^9$/L and 8.58 ± 5.72 $\times 10^9$/L, respectively ($p = 0.0020$). Lymphocyte counts were lower in the complicated group (1.45 ± 1.30 $\times 10^9$/L vs. 1.76 ± 1.04 $\times 10^9$/L; $p = 0.0492$). Mean platelet count was 402.99 ± 170.23 $\times 10^9$/L in the complicated group compared with 348.48 ± 130.25 $\times 10^9$/L in the uncomplicated group ($p = 0.0076$). Hemoglobin

was also significantly lower in patients with complications (10.16 ± 3.47 g/dL vs. 11.80 ± 3.17 g/dL; p = 0.0004).

The NLR was 10.08 ± 6.06 in the complicated group and 6.10 ± 5.62 in the uncomplicated group (p < 0.0001). The SII was 4754.79 ± 5234.87 in patients with complications compared with 2208.20 ± 2385.62 in those with an uncomplicated course (p < 0.0001), and the PLR was 416.67 ± 365.73 versus 258.85 ± 181.38, respectively (p < 0.0001). Similary CRP levels were significantly higher in patients who developed postoperative complications than in those with an uncomplicated postoperative course (144.75 ± 116.32 mg/L vs. 52.45 ± 58.27 mg/L, p < 0.0001).

Serum creatinine was 1.56 ± 0.90 mg/dL in the complicated group and 1.02 ± 0.52 mg/dL in the uncomplicated group (p < 0.0001). Urea was also significantly higher (67.97 ± 43.31 mg/dL vs. 49.10 ± 33.60 mg/dL; p = 0.0003).

7.6. Type and Severity of Complications

The most frequent complications recorded were related to the surgical wound, identified in 67 patients. Superficial wound infection occurred in 40 patients (18.10% of the cohort), complete wound dehiscence with evisceration in 12 (5.43%), and contained evisceration in 7 (3.17%). Skin ischemia and supra-aponeurotic seroma were each recorded in 4 patients (1.81%), and an abdominal-wall hematoma in 1 patient (0.45%).

Anastomotic leakage was identified in 30 patients (13.6% of the overall cohort). Stoma-related complications occurred in 22 patients, including ischemia of the bowel segment in 13 and peristomal abscesses in 9.

Among the 90 patients with complications, 35 (38.89%) had low-severity complications managed conservatively or by procedures performed under local anesthesia. The remaining patients required surgery, developed organ dysfunction, or died. The overall reoperation rate was 26.2%, with anastomotic leakage being the main indication.

The mean length of hospital stay was 10.49 ± 7.28 days. Patients with complications had a longer mean hospital stay than those without complications (13.75 ± 10.26 vs. 9.39 ± 5.57 days; p = 0.003).

7.7. Histopathological Characteristics and Postoperative Outcomes

Most patients had stage III disease, with 137 cases (61.99%). Stage II disease was identified in 74 patients (33.48%) and stage IV disease in 10 patients (4.53%). T4 tumors were

significantly more frequent in the complicated group than in the uncomplicated group (67.8% vs. 45.8%; p = 0.0012).

N0 disease was more frequent in the uncomplicated group than in the complicated group (45.8% vs. 17.8%). N2 disease was identified in 45.6% of patients with complications and 21.4% of those without complications, while N3 disease was present in 7.8% and 0.8%, respectively (p < 0.0001).

Tumor differentiation also differed significantly between groups, with poorly differentiated tumors being more frequent among patients with a complicated postoperative course. Lymphovascular and perineural invasion did not differ significantly.

7.8. Ability of Markers to Predict Severe Complications

ROC analysis demonstrated the predictive value of inflammatory markers for severe complications. CRP had the best individual performance, with an AUC of 0.818 (95% CI, 0.754–0.882), sensitivity of 82.1%, and specificity of 73.3%. The SII had an AUC of 0.752, sensitivity of 71.4%, and specificity of 68.5%. The NLR had an AUC of 0.747, sensitivity of 76.8%, and specificity of 66.1%, while the PLR had an AUC of 0.728, sensitivity of 69.6%, and specificity of 73.3%. All values were statistically significant (p < 0.001).

For surgical wound complications, CRP had the best discriminatory ability, with an AUC of 0.740 and a cutoff of 22.93 mg/L. For anastomotic leakage, the SII had an AUC of 0.749, and for stoma-related complications it had an AUC of 0.787, with a sensitivity of 81.8% at a cutoff of 2109.64.

In the multivariable logistic regression model, which included the Charlson score, type 2 diabetes mellitus, serum CRP, and SII, all four parameters were independent predictors of severe postoperative complications. The Charlson score had an OR of 1.361 (p = 0.007), type 2 diabetes an OR of 3.592 (p = 0.002), and CRP an OR of 1.007 (p = 0.003); the SII also remained statistically significant (p = 0.004). The model had an AUC of 0.877 (95% CI, 0.826–0.928; p < 0.001).

7.9. Factors Associated With Stoma Formation

Patients who underwent stoma formation were older than those who underwent anastomosis (71.40 ± 12.19 vs. 68.01 ± 10.99 years; p = 0.0347). The Charlson score was 7.11 ±

1.88 in the stoma group and 6.42 ± 1.94 in the anastomosis group (p = 0.0110).

Vasopressor therapy was required in 48.81% of patients with a stoma and 9.77% of those with an anastomosis (p < 0.0001). Organ failure was present in 53.57% and 15.79%, respectively (p < 0.0001).

Peritonitis was identified in 30.95% of patients with a stoma and 10.53% of those with an anastomosis (p = 0.0001). SIRS was present in 47.62% and 13.53%, respectively (p < 0.0001).

Inflammatory marker values differed between patients who underwent anastomosis and those who underwent stoma formation. The NLR was 10.32 ± 7.06 in the stoma group and 6.12 ± 4.86 in the anastomosis group (p < 0.0001). The SII was 4354.68 ± 4606.72 versus 2527.03 ± 3451.16 (p = 0.0010), and the PLR was 372.68 ± 333.91 versus 289.58 ± 240.19, respectively (p = 0.0344). Mean CRP was 135.09 ± 121.80 mg/L in the stoma group and 59.94 ± 62.50 mg/L in the anastomosis group (p < 0.0001). Creatinine was 1.45 ± 0.76 mg/dL and 1.10 ± 0.72 mg/dL, respectively (p = 0.0008).

Assessment of the predictive ability of preoperative parameters showed that the NLR had the best individual performance in distinguishing patients who underwent stoma formation from those who underwent primary anastomosis, with an AUC of 0.701, followed by CRP (AUC = 0.687), the SII (AUC = 0.686), and serum creatinine (AUC = 0.669). Cutoff values associated with stoma formation were NLR ≥ 6.84, SII ≥ 1711.79, CRP ≥ 95.18 mg/L, creatinine ≥ 1.26 mg/dL, and PLR ≥ 280.74. In multivariable logistic regression, the NLR, serum creatinine, hemoglobin, and BMI were identified as independent factors associated with stoma formation. The resulting model showed very good predictive ability, with an AUC of 0.840 (95% CI, 0.780–0.900; p < 0.001).

7.10. Predictors of Anastomotic Leakage

Anastomotic leakage occurred in 15.90% of the 132 patients with a primary anastomosis and complete postoperative data. Its occurrence was associated with SIRS, peritonitis, organ failure, vasopressor use, and a BMI ≥ 30 kg/m².

Among the laboratory markers, CRP showed the best predictive performance for anastomotic leakage, with an AUC of 0.890. Creatinine had an AUC of 0.846, the SII 0.835, the NLR 0.820, and the PLR 0.805. Blood glucose had an AUC of 0.755. The cutoff values were CRP ≥ 67.14 mg/L, with 85.7% sensitivity and 81.1% specificity; creatinine ≥ 0.93 mg/dL; SII ≥ 1828.03; NLR ≥ 6.54; PLR ≥ 336.56; and blood glucose ≥ 117.65 mg/dL. In the multivariable

model, creatinine had an OR of 2.074 ($p = 0.005$), and the SII remained an independent predictor ($p = 0.049$). The model had an AUC of 0.766 (95% CI, 0.679–0.854; $p < 0.001$).

7.11. Postoperative Mortality

Overall mortality was 25.8%, with 56 deaths. Abdominal or pulmonary sepsis was the leading cause and accounted for 41 deaths, while acute cardiovascular events accounted for 15 deaths.

Postoperative mortality was associated with SIRS (OR = 19.86), peritonitis (OR = 12.41), organ failure (OR = 14.86), vasopressor therapy (OR = 45.10), and obesity (OR = 2.57). Analysis of laboratory parameters showed an AUC of 0.754 for CRP, 0.734 for both creatinine and the NLR, and 0.727 for the SII in predicting postoperative mortality. Cutoff values associated with the risk of death were CRP ≥ 95.18 mg/L, creatinine ≥ 1.26 mg/dL, NLR ≥ 6.89, and SII ≥ 1828.03. In the multivariable model, peritonitis had an OR of 6.895 ($p < 0.001$), creatinine an OR of 1.783 ($p = 0.026$), and the SII remained significant ($p = 0.015$).

7.12. Survival Analysis

Mean survival was 8.06 days in the extended-procedure group and 10.66 days in the standard-resection group. Median survival was 5 days after extended procedures and 7 days after standard resections. The difference was not statistically significant ($p = 0.321$). Among patients with a stoma, mean survival was 8.34 days compared with 13.87 days among patients with a primary anastomosis.

8. Discusions

Emergency surgery for colon cancer carries substantial morbidity and mortality. Compared with elective surgery, there is limited time for comprehensive staging and optimization of the patient's physiological status. Therefore, management must prioritize control of the acute complication while preserving oncological radicality whenever feasible [24]. Moreover, the surgical insult may exacerbate pre-existing systemic inflammation, thereby promoting organ dysfunction and increasing the risk of adverse postoperative outcomes [25].

The study cohort consisted predominantly of elderly patients, with a mean age of approximately 70 years and a high prevalence of cardiovascular comorbidities, diabetes mellitus, and heart failure. Approximately one-third had organ failure at admission, and one-quarter met the SIRS criteria or required vasopressor support. These characteristics describe a population with limited physiological reserve in whom the effects of the tumor and acute complication are

amplified by the underlying biological condition. Accordingly, the overall surgical complication rate was 40.7%, consistent with the high morbidity reported in other emergency-surgery cohorts [26-28].

Tumor perforation had a greater prognostic impact than obstruction or hemorrhage. It was substantially more common among patients with a complicated course and was associated with a more than sevenfold increase in the risk of severe complications. In multivariable analysis, peritonitis remained an independent predictor of severe outcomes and mortality, with an OR of 6.895. This finding may be explained by the effects of peritoneal contamination, sepsis, hypoperfusion, and organ failure [29]. The presence of feculent fluid in the peritoneal cavity is therefore recognized as an unfavorable prognostic factor and is associated with increased postoperative mortality.

Systemic inflammation is the central element linking carcinogenesis, the severity of the acute complication, and postoperative outcomes. Tumor cells and inflammatory cells within the tumor microenvironment release IL-1, IL-6, IL-8, IL-17, TNF-α, and chemokines, promoting neutrophil and macrophage recruitment, angiogenesis, and extracellular matrix remodeling [30]. In complicated colon cancer, the inflammatory response is amplified by intestinal ischemia, bacterial translocation, and peritoneal contamination, leading to an exaggerated inflammatory response and activation of the coagulation cascade, which promote microthrombosis, hypoperfusion, and impaired healing [25,31]. Consequently, the measured levels of individual inflammatory components may be substantially altered in these patients.

Patients who developed complications had significantly higher leukocyte, neutrophil, platelet, NLR, PLR, SII, CRP, urea, and creatinine values. CRP had the best individual performance for predicting severe complications, with an AUC of 0.818, sensitivity of 82.1%, and specificity of 73.3%. As an acute-phase reactant synthesized under the influence of IL-6, CRP rises rapidly in infection, ischemia, and trauma [32] and reflects endothelial activation, increased vascular permeability, and the development of a procoagulant, antifibrinolytic state. These mechanisms impair tissue perfusion and repair [33-35], thereby increasing the likelihood of postoperative complications.

The NLR reflects the relationship between activation of innate immunity and suppression of the adaptive immune response. Neutrophilia promotes oxidative stress, angiogenesis, and tumor progression, whereas lymphopenia reflects reduced immune surveillance [36-38]. In both

cohorts, the NLR was significantly higher in patients with severe complications and was associated with stoma formation, anastomotic leakage, and higher postoperative mortality. These results are consistent with studies linking an elevated NLR to advanced disease, ischemic complications, and early mortality [39-41].

The SII integrates neutrophils, lymphocytes, and platelets and provides an overall assessment of inflammation, immunosuppression, and prothrombotic status [42]. It remained an independent predictor in models for severe postoperative complications, anastomotic leakage, and postoperative mortality. For every 100-unit increase in the SII, the risk of severe complications increased by approximately 1.7%. Incorporating this parameter into a multivariable model including the Charlson score, diabetes mellitus, CRP, and SII yielded an AUC of 0.877, demonstrating very good ability to identify patients at risk of severe complications. This is one of the most important findings of the study because it confirms the superiority of integrated assessment over the isolated use of a single biomarker.

Among the clinical parameters, the Charlson score and diabetes mellitus were independent predictors of severe complications. Each one-point increase in the Charlson score was associated with an approximately 36% increase in the risk of a complicated postoperative course, while diabetes was associated with a 3.6-fold increase in risk. Impaired chemotaxis and phagocytosis, microvascular dysfunction, and delayed tissue repair in tissues chronically exposed to elevated glucose levels may explain the increased risk of postoperative complications. These findings are supported by a meta-analysis of more than 93,000 patients undergoing colorectal surgery, which found increased rates of anastomotic leakage, infection, and mortality among patients with diabetes [43].

Patients who underwent stoma formation after resection more frequently had peritonitis, SIRS, organ failure, and vasopressor requirements, as well as higher inflammatory marker and creatinine levels. The NLR had the best individual performance in distinguishing stoma formation from primary anastomosis, with an AUC of 0.701. For every one-unit increase in the NLR, the probability of stoma formation increased by 11.4%.

The model comprising the NLR, creatinine, hemoglobin, and BMI had an AUC of 0.84, indicating very good predictive ability for intraoperative management. This finding shows that the choice of a stoma was influenced not exclusively by tumor location or stage, but primarily by the patient's biological severity. The absence of an association with T and N stage, histological

type, and lymphovascular or perineural invasion supports this observation. The higher reoperation and mortality rates in the stoma group should therefore not be interpreted as a direct adverse effect of the procedure. Rather, the data suggest that stomas were created in patients with profoundly impaired clinical and biological ststus and should be regarded as a marker of baseline severity rather than a cause of unfavorable outcomes.

Although primary anastomosis was performed in 62.3% of patients, anastomotic leakage occurred in 15.9% and was associated with SIRS, peritonitis, organ failure, vasopressor use, and obesity. Among the laboratory markers analyzed, CRP had the best performance, with an AUC of 0.890. A cutoff of 67.14 mg/L provided 85.7% sensitivity and 81.1% specificity. The SII had an AUC of 0.835 and creatinine an AUC of 0.846, and both remained independent predictors in multivariable analysis. The association between inflammation and anastomotic leakage may be explained by the effects of effector cells on the extracellular matrix and microcirculation. Neutrophils and macrophages stimulate metalloproteinases, reducing the structural support required for fibroblast migration, while microthrombosis and hypoperfusion compromise anastomotic vascularization [44,45].

Overall mortality was 25.8%, with abdominal or pulmonary sepsis and acute cardiovascular events being the main causes. SIRS, peritonitis, organ failure, and vasopressor use showed the strongest associations with death. For postoperative mortality risk, CRP had an AUC of 0.754, creatinine and the NLR each had an AUC of 0.734, and the SII had an AUC of 0.727. Cutoffs associated with increased risk were CRP ≥ 95.18 mg/L, creatinine ≥ 1.26 mg/dL, NLR ≥ 6.89, and SII ≥ 1828.03. In the multivariable model, peritonitis, creatinine, and the SII remained independent predictors of postoperative mortality.

Overall, the results demonstrate that CRP is the best-performing individual marker for severe complications and anastomotic leakage, the NLR is the most useful marker for guiding the choice between primary anastomosis and stoma formation, and the SII has the most consistent independent value for severe complications, leakage, and mortality. Integrating these markers with the Charlson score, diabetes mellitus, and renal function provides superior preoperative risk stratification.

The main limitations of this research are its retrospective, single-center design, the heterogeneity of the procedures, and variability among surgical teams. The identified cutoff values are exploratory and require prospective, multicenter validation. Nevertheless, a major

strength is the use of simple, inexpensive, and rapidly available parameters that may contribute to individualized surgical management and early identification of high-risk patients.

9. References

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List of Published Papers

1. **Colonic Stenting as a Bridge to Surgery Versus Emergency Resection in Obstructive Colon Cancer: A Systematic Review of Surgical Outcomes**
   Silaghi AM, Grigorescu CC, Serban D, Tribus LC, Constantin VD, Motofei I, Dumitrescu D, Tudor C, Dumitrescu V, Cristea BM, et al. Published in the *Journal of Clinical Medicine*, an ISI-indexed journal with an impact factor of 3.3. Available at: https://www.mdpi.com/2077-0383/15/12/4416
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3. **Clinical and Inflammatory Biomarkers Predicting Emergency Surgical Management Decisions and Postoperative Outcomes in Complicated Colon Cancer**
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